

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in this application.

Listing of Claims:

Claim 1 (Currently Amended). A transgenic ~~non-~~
~~human-mammal~~ mouse whose genome comprises a transgene
comprising a nucleotide sequence operably linked to a promoter
and encoding a heterologous amyloid precursor protein 695
(APP695) polypeptide wherein the lysine residue at position
670 is substituted by asparagine, the methionine residue at
position 671 is substituted by leucine and the valine residue
at position 717 is substituted by phenylalanine and wherein
~~the transgene is expressed~~ said promoter directs central
nervous system or neuronal expression of said transgene.

Claim 2 (Cancelled).

Claim 3 (Currently Amended). The transgenic
mouse of ~~claim 2~~ claim 1 wherein the mouse is a (C3H x C57
BL6) x C57 mouse.

Claim 4 (Original). The transgenic mouse of claim 3 wherein the heterologous APP695 is human APP695.

Claim 5 (Original). The transgenic mouse of claim 4 wherein the mouse displays abnormal A β deposition in its central nervous system.

Claim 6 (Previously Presented). The transgenic mouse of claim 4 wherein the animal displays an appearance of Alzheimer's Disease-related pathology by 3 months of age.

Claim 7 (Previously Presented). A mouse having the transgenic mouse of claim 4 as an ancestor, wherein the mouse comprises said transgene.

Claim 8 (Withdrawn-Currently Amended). A transgenic ~~non-human-mammal~~ mouse produced by:

(a) crossing a first transgenic ~~non-human-mammal~~ mouse in accordance with claim 1 with a second ~~non-human-mammal~~ mouse having a genome comprising a second gene comprising a nucleotide sequence operably linked to a promoter and encoding a selected protein having at least one selected mutation to produce first generation offspring; and

(b) selecting from the first generation offspring a transgenic ~~non-human-mammal~~ mouse having a genome comprising at least one first transgene comprising a nucleotide sequence operably linked to a promoter and encoding a heterologous APP695 polypeptide wherein the lysine residue at position 670 is substituted by asparagine, the methionine residue at position 671 is substituted by leucine and the valine residue at position 717 is substituted by phenylalanine and at least one second gene comprising a nucleotide sequence operably linked to a promoter and encoding said selected protein having at least one selected mutation and expressing both said at least one first transgene and said at least one second gene.

Claim 9 (Withdrawn-Currently Amended). The transgenic ~~non-human-mammal~~ mouse of claim 8 wherein the selected protein is a presenilin and the selected mutation is an AD-related mutation.

Claim 10 (Withdrawn-Currently Amended). The transgenic ~~non-human-mammal~~ mouse of claim 8 wherein the selected protein is selected from the group consisting of a low density lipoprotein receptor related gene, an α 2-

macroglobulin gene and a β -secretase gene and the selected mutation is an A β processing-related mutation.

Claim 11 (Withdrawn). The transgenic non-human mammal of claim 10 wherein the mammal is a mouse.

Claim 12 (Withdrawn). A transgenic mouse produced by:

(a) crossing a first transgenic mouse in accordance with claim 4 with a second mouse having a genome comprising a second gene comprising a nucleotide sequence operably linked to a promoter and encoding a selected protein having at least one selected mutation to produce first generation offspring; and

(b) selecting from the first generation offspring a transgenic mouse having a genome comprising at least one first transgene comprising a nucleotide sequence operably linked to a promoter and encoding a heterologous APP695 polypeptide wherein the lysine residue at position 670 is substituted by asparagine, the methionine residue at position 671 is substituted by leucine and the valine residue at position 717 is substituted by phenylalanine and at least one second gene comprising a nucleotide sequence operably

linked to a promoter and encoding said selected protein having at least one selected mutation and expressing both said at least one first transgene and said at least one second gene.

Claim 13 (Withdrawn). The transgenic mouse of claim 12 wherein the second gene is a mutant endogenous gene.

Claim 14 (Withdrawn). The transgenic mouse of claim 12 wherein the second gene is a transgene.

Claim 15 (Withdrawn). The transgenic mouse of claim 12 wherein the second gene comprises a nucleotide sequence encoding a selected protein having an AD-related amino acid substitution.

Claim 16 (Withdrawn). The transgenic mouse of claim 15 wherein the selected protein is a presenilin.

Claim 17 (Withdrawn). The transgenic mouse of claim 12 produced by:

(a) crossing a first transgenic mouse in accordance with claim 4 with a second transgenic mouse having a genome comprising a transgene comprising a nucleotide

sequence operably linked to a promoter and encoding a heterologous presenilin 2 polypeptide wherein the methionine residue at position 239 is substituted by valine to produce first generation offspring; and

(b) selecting from the first generation offspring a transgenic mouse having a genome comprising at least one first transgene comprising a nucleotide sequence operably linked to a promoter and encoding a heterologous amyloid precursor protein (APP) polypeptide wherein the lysine residue at position 670 is substituted by asparagine, the methionine residue at position 671 is substituted by leucine and the valine residue at position 717 is substituted by phenylalanine and at least one second transgene comprising a nucleotide sequence operably linked to a promoter and encoding a heterologous presenilin 2 polypeptide wherein the methionine residue at position 239 is substituted by valine and expressing both said first and second transgenes.

Claim 18 (Withdrawn). The transgenic mouse of claim 12 produced by:

(a) crossing a first transgenic mouse in accordance with claim 4 with a second transgenic mouse having a genome comprising a transgene comprising a nucleotide

sequence operably linked to a promoter and encoding a heterologous presenilin 1 polypeptide wherein the leucine residue at position 286 is substituted by valine to produce first generation offspring; and

(b) selecting from the first generation offspring a transgenic mouse having a genome comprising at least one first transgene comprising a nucleotide sequence operably linked to a promoter and encoding a heterologous amyloid precursor protein (APP) polypeptide wherein the lysine residue at position 670 is substituted by asparagine, the methionine residue at position 671 is substituted by leucine and the valine residue at position 717 is substituted by phenylalanine and at least one second transgene comprising a nucleotide sequence operably linked to a promoter and encoding a heterologous presenilin 1 polypeptide wherein the leucine residue at position 286 is substituted by valine and expressing both said first and second transgenes.

Claim 19 (Withdrawn). The transgenic mouse of claim 12 produced by:

(a) crossing a first transgenic mouse in accordance with claim 4 with a second transgenic mouse having a genome comprising a transgene comprising a nucleotide

sequence operably linked to a promoter and encoding a heterologous presenilin 1 polypeptide wherein the methionine residue at position 146 is substituted by leucine and the leucine residue at position 286 is substituted by valine to produce first generation offspring; and

(b) selecting from the first generation offspring a transgenic mouse having a genome comprising at least one first transgene comprising a nucleotide sequence operably linked to a promoter and encoding a heterologous amyloid precursor protein (APP) polypeptide wherein the lysine residue at position 670 is substituted by asparagine, the methionine residue at position 671 is substituted by leucine and the valine residue at position 717 is substituted by phenylalanine and at least one second transgene comprising a nucleotide sequence operably linked to a promoter and encoding a heterologous presenilin 1 polypeptide wherein the methionine residue at position 146 is substituted by leucine and the leucine residue at position 286 is substituted by valine and expressing both said first and second transgenes.

Claim 20 (Withdrawn). A method for screening a candidate compound for its efficacy in preventing or delaying the development of AD, the method comprising the steps of:

(a) administering the candidate compound to a first transgenic mouse in accordance with any one of claims 1 to 19 prior to the appearance of a selected AD-related phenotypic trait in said mouse; and

(b) comparing the age at which said selected AD-related phenotypic trait appears in said mouse with the age at which said trait appears in a second transgenic mouse of the same type to which the compound had not been administered; wherein an increased age of appearance of the trait in the first mouse compared to that in the second mouse indicates efficacy of the compound.

Claim 21 (Withdrawn). The method of claim 20 wherein the trait is a behavioral deficit.

Claim 22 (Withdrawn). The method of claim 20 wherein the trait is abnormal CNS amyloid deposition.

Claim 23 (Withdrawn). A method for screening a candidate compound for its efficacy in ameliorating the symptoms of Alzheimer's Disease, the method comprising the steps of:

(a) administering the candidate compound to a first transgenic mouse in accordance with any one of claims 1 to 19;

(b) determining the performance of said mouse in a memory or learning test; and

(c) comparing the performance of said mouse with the performance of a second transgenic mouse of the same type to which the compound has not been administered; wherein an improved performance of the first mouse compared to that of the second mouse indicates efficacy of the compound.

Claim 24 (Currently Amended). A method of producing a transgenic ~~non-human-mammal~~ mouse that displays abnormal A β deposition in its central nervous system comprising:

(a) introducing into a fertilized oocyte of said ~~mammal~~ mouse a transgene comprising a nucleotide sequence operably linked to a promoter and encoding a heterologous amyloid precursor protein 695 (APP695) polypeptide wherein the lysine residue at position 670 is substituted by asparagine, the methionine residue at position 671 is substituted by leucine and the valine residue at position 717 is substituted

by phenylalanine and wherein said promoter directs central nervous system or neuronal expression of said transgene;

(b) transplanting said fertilized oocyte into a pseudopregnant ~~mammal~~ mouse;

(c) allowing said fertilized oocyte to develop into a live born offspring; and

(d) selecting an offspring where genome comprises a transgene comprising a nucleotide sequence operably linked to a promoter and encoding a heterologous amyloid precursor protein 695 (APP695) polypeptide wherein the lysine residue at position 670 is substituted by asparagine, the methionine residue at position 671 is substituted by leucine and the valine residue at position 717 is substituted by phenylalanine and wherein the transgene is expressed.

Claim 25 (Cancelled).

Claim 26 (Original). The method of claim 24 wherein the promoter is the prion protein cos.Tet promoter.

Claim 27 (Original). A nucleotide sequence encoding a heterologous amyloid precursor protein 695 (APP695) polypeptide wherein the lysine residue at position 670 is

substituted by asparagine, the methionine residue at position 671 is substituted by leucine and the valine residue at position 717 is substituted by phenylalanine.

Claim 28 (Original). A vector comprising the nucleotide sequence of claim 27 operably linked to a promoter.

Claim 29 (Withdrawn-Currently Amended). A method of reducing a cognitive deficit in a ~~mammal~~ mouse which suffers from abnormal amyloid deposition in its central nervous system, the method comprising administering to the ~~mammal~~ mouse an amount of an A β peptide effective to reduce the cognitive defect.

Claim 30 (Withdrawn). The method of claim 29 wherein the abnormal amyloid deposition is A β deposition.

Claim 31 (Withdrawn). The method of claim 29 or 30 wherein the administered peptide is A β 42.

Claim 32 (Withdrawn). The method of any one of claims 29 to 31 wherein the mammal is a human suffering from Alzheimer's Disease.

Claim 33 (Withdrawn). Use of an A β peptide to manufacture a medicament for reducing a cognitive deficit in a mammal which suffers from abnormal amyloid deposition in its nervous system.

Claim 34 (Withdrawn). The use of claim 33 wherein the A β peptide is A β 42.

Claim 35 (Withdrawn). The use of claim 33 or 34 wherein the medicament is for the prevention or treatment of Alzheimer's Disease.

Claim 36 (New). The transgenic mouse according to claim 1, wherein said promoter is selected from the group consisting of: the neuron specific enolase gene promoter; the human platelet derived growth factor B subunit promoter; the Thy-1 promoter; the neurofilament promoter; and the cosTet prion promoter.

Claim 37 (New). The method according to claim 24, wherein said promoter is selected from the group consisting of: the neuron specific enolase gene promoter; the

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human platelet derived growth factor B subunit promoter; the
Thy-1 promoter; the neurofilament promoter; and the costet
prion promoter.